The medical treatment of cardiogenic shock: cardiovascular drugs

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Purpose of review
To discuss the use of vasopressors and inotropes in cardiogenic shock.

Recent findings
The classic form or cardiogenic shock requires administration of inotropic and/or vasopressor agents to try to improve the impaired tissue perfusion. Among vasopressors various alpha-adrenergic agents, vasopressin derivatives and angiotensin can be used. The first-line therapy remains norepinephrine as it is associated with minimal adverse effects and appears to be associated by the best outcome in network meta-analyses. On the contrary, epinephrine is associated with an increased incidence of refractory shock and observational studies suggest an increased risk of death. Vasopressin may be an excellent alternative in tachycardiac patients or in the presence of pulmonary hypertension. Concerning inotropic agents, dobutamine is the first-line agent but levosimendan is an excellent alternative or additional agent in cases not responding to dobutamine. The impact on outcome of inotropic agents remains controversial.

Summary
Recent studies have refined the position of the various vasopressor and inotropic agents. Norepinephrine is recommended as first-line vasopressor agent by various guidelines. Among inotropic agents, selection between the agents should be individualized and based on the hemodynamic response.

Keywords
cardiac output, catecholamines, inotropic, phosphodiesterase inhibitors, vasopressor agent

INTRODUCTION

Cardiogenic shock is a form of circulatory failure in which the cardiac pump is unable to deliver enough cardiac output so that oxygen delivery to the tissues becomes insufficient to meet their basal metabolism, resulting in tissue dysoxia [1,2]. It is the second most frequent type of circulatory failure [3]. Although the low cardiac output despite adequate cardiac preload is the most obvious hemodynamic manifestation of cardiogenic shock [4▪▪], many non-surviving patients with cardiogenic shock die despite correction of cardiac output [5]. A decrease in vascular tone is often observed [3], resulting in a decrease in the perfusion pressure of the organs. In addition, microvascular alterations may be observed despite correction of low cardiac output syndrome and hypotension [6]. These contribute to the impairment in tissue perfusion and are associated with a poor outcome [6,7▪,8].

The goal of hemodynamic resuscitation in cardiogenic shock is to improve cardiac output and blood pressure, in order to preserve tissue perfusion, without compromising myocardial energetics. In addition to preload optimization, vasopressor and inotropic agents are often used. In this review, we will describe the evidence supporting the use of various vasopressor and inotropic agents.

VASOPRESSOR AGENTS

Vasopressor agents are used to increase mean arterial pressure (MAP) in order to restore tissue perfusion

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KEY POINTS

- Noradrenaline is the first-line vasopressor agent as it increases blood pressure and is associated with minimal adverse effects
- Epinephrine is associated with excessive tachycardia and may favor arrythmias and refractory shock
- Vasopressin may be an alternative to norepinephrine in patients with tachycardia or with pulmonary hypertension
- Among inotropic agents, dobutamine remains the first-line agent. Phosphodiesterase inhibitors and levosimendan may be excellent alternatives in selected cases.

pressure. Vasopressor agents may also improve coronary artery perfusion pressure by increasing diastolic pressure. However, the beneficial effects of increasing tissue perfusion pressure and coronary perfusion pressure may be balanced by the increase in left ventricular afterload. In addition, some vasopressor agents may further deteriorate myocardial energetics by increasing heart rate (Fig. 1). Although the pressor effect is relatively similar with the various vasopressor agents, the increase in myocardial work and the ability of the heart to sustain the increase in afterload vary according to the type of vasopressor agent.

Adrenergic agents, vasopressin derivatives and angiotensin stimulate specific surface receptors (alpha adrenergic, vasopressin 1, and angiotensin 2 receptors), but the mechanisms leading to constriction are identical with these agents. Although in normal conditions stimulation of any of the three surface receptors results in an increase in MAP, down-regulation may variably affect the three types of receptors explaining why some patients may respond preferentially to some vasopressor agents. In addition, differences in the density of the various surface receptors in different vascular beds explain differences in regional hemodynamics between the agents. Finally, co-stimulation of other receptors (beta-adrenergic receptors, vasopressin2 receptors, etc.) may induce some favorable or detrimental hemodynamic or metabolic effects. Although adrenergic agents, and in particular noradrenaline, are considered as first-line vasopressor agents [4▪▪,9▪], alternative agents such as vasopressin derivatives and angiotensin should be considered taking into account the response to the first-line agent and the specificities of the patient.

Adrenergic vasopressors

Alpha1 adrenoreceptors are present in the systemic and pulmonary circulation. Stimulation of alpha1 receptors increase systemic and pulmonary artery pressure. Interestingly alpha1 adrenoreceptors are also expressed in myocardium, even though less abundant than beta adrenoreceptors [10▪]. Stimulation of myocardial alpha1 adrenoreceptors enhances calcium entry and increases contractility [11]. However, the inotropic effect of the alpha-adrenergic receptors is quite limited so that pure alpha-adrenergic stimulation may result in a decrease in cardiac output if the heart is unable to cope with the increase in left and right ventricular afterload. Some adrenergic agents also stimulate beta-adrenergic and dopaminergic receptors. Although the dopaminergic

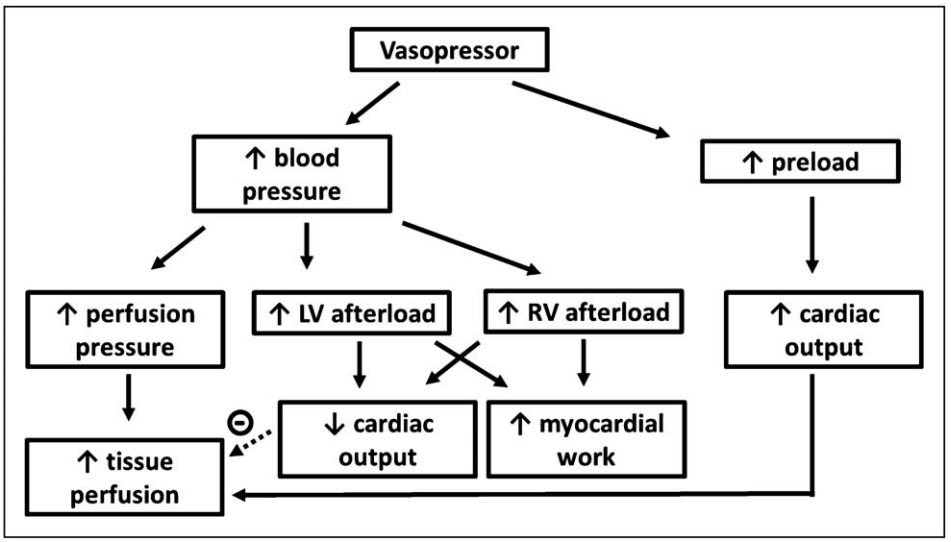

FIGURE 1. The hemodynamic and metabolic effects of vasopressor agents.

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receptors have limited impact on cardiac inotropy, beta adrenergic receptors have strong inotropic, chronotropic, and luisotropic effects.

The hemodynamic and metabolic properties of dopamine, norepinephrine, epinephrine, and phenylephrine differ according to their associated beta-adrenergic effect. The beta-adrenergic effect is minimal with norepinephrine, important with epinephrine and dopamine, and absent with phenylephrine. Accordingly, dopamine and epinephrine increase both cardiac output and blood pressure, norepinephrine increases blood pressure with modest impact on cardiac output and phenylephrine increases blood pressure but may decrease cardiac output. In patients with cardiogenic shock, the minimal beta-adrenergic effect is likely to be beneficial by counteracting the increase in afterload induced by vasopressor agents, however, the excessive beta-stimulation may be detrimental by contributing to the development of arrhythmias, increased myocardial oxygen consumption and unfavorable metabolic effects.

The use of norepinephrine in cardiogenic shock was proposed in the 1950s [12] but concerns were raised about excessive vasoconstriction. Association with inotropic agents such as isoprenaline or dobutamine allowed to limit its potential negative impact on cardiac output and peripheral perfusion. In the seventies, dopamine appeared as an excellent alternative increasing both arterial pressure and cardiac output, with limited impact on oxygen consumption [13]. Up to the end of the last century, dopamine was considered as the first-line agent in cardiogenic shock [14].

A large-scale multicentric randomized trial comparing dopamine and norepinephrine reported that dopamine was associated with a 10% increase in heart rate ($P < 0.0001$) and a significant increase in arrhythmic events (24 vs 12%, $P < 0.0001$) [15]. In the subgroup of 280 patients with cardiogenic shock, dopamine was associated with a significant increase in mortality [15]. These results were confirmed in a recent meta-analysis [16]. Accordingly, recent guidelines now recommend the use of norepinephrine as first-line vasopressor agent in cardiogenic shock patients [9▪].

On theoretical basis, epinephrine looks like an excellent choice in cardiogenic shock, whereas its strong alpha-adrenergic properties allow to correct hypotension, the strong beta-adrenergic effect may allow to preserve or increase cardiac output despite the increase in afterload.

At low doses, the use of epinephrine is associated with beneficial effects, increasing heart contractility and coronary artery perfusion, with minimal impact on metabolism [17]. However higher doses may be associated with adverse events including tachycardia and arrythmias, increased left ventricular work, impaired myocardial metabolism in association with detrimental peripheral effects.

Small size randomized trials compared the effects of epinephrine and norepinephrine in patients with cardiogenic shock. In a single-center study including 30 hypotensive patients with non-ischemic cardiogenic shock, short-term (24 h) infusions of epinephrine and norepinephrine, titrated to achieve the same target pressure, similarly increased cardiac index, oxygen delivery, and oxygen consumption [18]. However, epinephrine administration was associated with more arrhythmic events, a rise in lactate levels and in gastric mucosal PCO_2 and a lower diuresis compared to norepinephrine [18]. A multicentric trial in patients with cardiogenic shock due to acute myocardial infarction was prematurely terminated after inclusion 57 patients, due to a higher incidence of development of refractory shock in the epinephrine group (37% in the epinephrine group vs 7% in the norepinephrine group, $P = 0.008$) [19]. Heart rate increased significantly in epinephrine, whereas it remained stable with norepinephrine. Stroke volume index and cardiac power index increased similarly with the two agents but cardiac double product, reflecting myocardial oxygen consumption, increased in the epinephrine group only. Epinephrine was associated with gastric mucosal and lactic acidosis, and with a trend to higher use of renal replacement therapy (26% vs 7%, $P = 0.07$), ECLS implantation (11% vs 3%, $P = 0.28$) and a higher risk of death at 60 days (52% vs 37%, $P = 0.25$). These two randomized trials strongly suggest that epinephrine may be associated with unfavorable hemodynamic and metabolic effects, and to the development of refractory shock. Association with mortality was not demonstrated in these small-size trials.

Observational studies suggest a detrimental effect of epinephrine in cardiogenic shock. In a multinational cohort of 219 patients with cardiogenic shock, the use of epinephrine was associated with worsening of renal function and increase in troponin levels [20]. Epinephrine administration was independently associated with 90-day mortality [20]. Aggregating data reported in 14 published cohorts and two unpublished data-sets, Leopold *et al.* [21] reported that epinephrine use was associated with an increased risk of death in patients with cardiogenic shock. In a cohort of 168 patients with cardiogenic shock, norepinephrine was associated with a lower risk of death compared to patients receiving epinephrine or dopamine [22].

Altogether these data suggest that noradrenaline is the adrenergic vasopressor agent of choice.

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What option should be retained when patients fail to respond to norepinephrine? The use of another adrenergic vasopressor agent seems not to be the best option: stimulation of alpha-adrenergic receptor will not be more effective with the alternative agents compared to norepinephrine while the adverse events will be increased. It sounds logical to add an agent of another class when the patient remains hypotensive despite use of high doses of norepinephrine.

Vasopressin derivatives

Vasopressin 1 receptor stimulation is associated with a vasopressor effect. It has no inotropic or chronotropic effect. Vasopressin may limit the increase in endothelial permeability.

The distribution of vasopressin receptors among the vascular tree is not homogeneous. There is higher density of receptors in systemic than in pulmonary circulation so that the rise in systemic vascular resistance is higher than its pulmonary counterpart. Also, vasopressin receptors density is higher in efferent than afferent renal arterioles, which may selectively increase glomerular filtration pressure. On the other hand, vasopressin receptors are also highly present in mesenteric circulation, which may result in splanchnic ischemia.

The place of vasopressin derivatives in cardiogenic shock is not straightforward and head-to-head comparison of vasopressin and adrenergic derivatives in large-scale trials is lacking. The absence of inotropic effect may be associated by a decrease in cardiac output if the heart is unable to sustain the raise in afterload, which is a real concern in low output states. On the other hand, the absence of chronotropic effect may be interesting in patients prone to develop arrythmias. The predominant systemic vasoconstrictive effect with minimal impact on pulmonary vasculature offers to vasopressin an interesting profile in patients with predominant right heart failure.

Angiotensin

Angiotensin is a newly rediscovered vasopressor agent. It was already used in the sixties to treat shock states, including cardiogenic shock [23]. Angiotensin may be associated with splanchnic ischemia [24] and renal dysfunction. The drug disappeared but was recently reintroduced. In a multicentric randomized trial, angiotensin was shown to significantly increase blood pressure in refractory shock, without significant adverse effects [25]. Its use in cardiogenic shock remains confidential with promising results in 38 cases collected in the literature [26]. Given the paucity of data, the use of angiotensin in patients with cardiogenic shock should be restricted to clinical trials.

Which target pressure in patients with cardiogenic shock?

Although observational studies have linked both severity and duration of hypotension with a poor outcome [27], the ideal blood pressure target for patients in cardiogenic shock remains debated. On one hand, reaching a higher blood pressure target may be associated with higher organ perfusion pressure but on the other hand this implies to use higher doses of vasopressor agents that exposes to higher risk of adverse events, increases afterload and cardiac work to a higher level, and may fail to improve microvascular perfusion.

In a series of 25 patients with cardiogenic shock due to myocardial infarction, increasing MAP from 65 to 85 mmHg was associated with an increase in cardiac index, left ventricular stroke work, and mixed-venous oxygen saturation together with a decrease in lactate levels [28]. In another series of patients, the increase in arterial pressure was not associated with an improvement in cerebral or peripheral tissue oxygenation [29].

In absence of clear evidence from randomized trials, blood pressure targets should thus be individualized, taking into account estimates of tissue perfusion and signs of myocardial (in)tolerance. Selection of MAP target and vasopressor agent is best guided by hemodynamic monitoring in patients with cardiogenic shock.

Which vasopressor in the context of mechanically supported heart?

In patients under mechanical support for cardiogenic shock, vasopressors are frequently used to maintain tissue perfusion pressure. In these patients, hypotension is related to a vasoplegic state related to the underlying condition, ischemia-reperfusion injury and blood-device related release of vasodilatory substances.

In mechanically supported hearts, some of the potentially negative effects of increasing afterload may be less relevant, even though it may depend on the device used.

Most of the evidence on the hemodynamic and metabolic effects of vasopressor agents in mechanically supported hearts comes from experimental studies.

Norepinephrine, epinephrine, dopamine and phenylephrine identically increased blood pressure in pigs assisted with Impella [30▪]. Dopamine and

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phenylephrine increased left ventricular work more than norepinephrine and epinephrine. In addition, phenylephrine failed to improve stroke volume and peripheral perfusion. In that model, the best balance was observed with low doses of norepinephrine and epinephrine.

Comparing vasopressin and norepinephrine in Extracorporeal Membrane Oxygenation (ECMO) sustained experimental cardiogenic shock, Klein *et al.* [31▪] reported that vasopressin blunted the increase in vascular permeability, was associated with a less positive fluid balance and limited pulmonary interstitial edema, compared to norepinephrine.

A feasibility trial reported the effects of angiotensin in seven patients supported by VA ECMO [32]. Angiotensin administration allowed to reduce norepinephrine doses with noticed adverse events. Further studies are required to evaluate the impact of angiotensin on cardiac function, tissue perfusion and tissue metabolism.

INOTROPIC AGENTS

In cardiogenic shock, tissue perfusion is critically impaired due to alteration in cardiac pump function. Inotropic agents should be considered when the impairment in contractile function is contributing to the low cardiac output responsible of the impaired tissue perfusion.

Adrenergic inotropic agents

Agents with strong beta-adrenergic properties have inotropic effects. Epinephrine and dopamine have predominant alpha-adrenergic properties and are thus considered as vasopressors rather than inotropic agents. Isoprenaline and dobutamine are the main adrenergic receptor agonists used for their inotropic properties. Isoprenaline has strong beta2 action that results in chronotropic and vasodilatory properties, in addition to its inotropic effect. It was mostly used in cardiogenic shock before the onset of dobutamine [33]. Dobutamine has a strong beta1 effect, associated with a minimal alpha1 effect. Accordingly, dobutamine increases heart contractility with limited effect on heart rate and blood pressure [34].

Although both agents increase myocardial oxygen consumption, this effect is mostly due to the increase in contractile function rather than to a direct cellular effect [35]. Interestingly, dobutamine improves mitochondrial function in noninfarcted myocardium, improving oxygen utilization efficiency [36].

In patients with cardiogenic shock, dobutamine increased cardiac index by an increase in stroke index more than in heart rate [13,37]. High doses (>20 mcg/kg min) should be avoided as associated with excessive tachycardia and an increase in metabolism (thermogenic effect, increased glycolysis) that may impair oxygen balance.

Although dobutamine is the most frequently used inotropic agent [38▪], its use is mostly supported by small size trials exploring the hemodynamic and metabolic effects of the drug. In trials comparing dobutamine to other inotropic agents no significant benefit was reported for one versus the other agent [39▪].

Phosphodiesterase inhibitors

Phosphodiesterase III inhibitors increase contractility by increasing intracellular cyclic AMP independently of stimulation of the beta-adrenergic receptor. Phosphodiesterase inhibitors can still be active in the presence of beta-blockade or when beta-adrenergic receptors are down-regulated [40]. Combining phosphodiesterase inhibitors with beta-adrenergic agents often result in a higher increase in cardiac output compared to each agent in isolation.

In addition to the inotropic effect phosphodiesterase inhibitors, these agents are also associated with systemic and pulmonary vasodilation. The decrease in blood pressure is a concern in cardiogenic shock and often require increase in doses of vasopressor agents. On the other hand, the pulmonary vasodilation may be beneficial in the context of right heart dysfunction.

The hemodynamic effects of phosphodiesterase inhibitors in cardiogenic shock have been described in small size studies [41]. The impact of phosphodiesterase inhibitors on the outcome of patients with cardiogenic shock has not been well studied [39▪]. Network meta-analysis including nonrandomized trial suggest some benefit for milrinone [42▪]. This was not confirmed in a randomized study comparing dobutamine and milrinone in 192 patients reported no difference in the primary composite end-point aggregating in-hospital mortality, nonfatal myocardial infarction, stroke, new initiation of renal replacement therapy, need for mechanical support device or cardiac transplant, or cardiac arrest with successful resuscitation [43▪▪].

Levosimendan

Levosimendan combines a phosphodiesterase inhibition activity with a direct calcium-sensitizing effect on troponin C. Levosimendan also opens ATP-dependent potassium channels in peripheral vascular smooth muscle cells leading to vasodilation. Levosimendan also acts on mitochondrial ATP-dependent potassium channels both in myocardium and peripheral tissues,

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potentially conferring some protective effects on ischemia/reperfusion injury [44▪].

The hemodynamic effects are consistent with an increase in contractility and decreases in vascular tone, both in systemic and pulmonary circulations. Several studies have shown that levosimendan increases cardiac output and decreases left ventricular filling pressures [45–47]. Of note its half-life is quite long [44▪], which may be an advantage in chronic heart failure but less advantageous in the context of more transient impairment in contractile function such as in acute myocardial infarction.

The impact of levosimendan on outcome is not well defined. Although meta-analyses suggest some benefit in survival in acute heart failure [39▪], the effects in cardiogenic shock remains less well defined [42▪].

Levosimendan may benefit for weaning patients from ECMO [48▪,49▪] but these effects are challenged [50▪,51▪]. A large-scale randomized trial is underway in order to better define the interest of levosimendan in this context (NCT04020263).

VASOPRESSOR OR INOTROPIC AGENTS: WHICH SHOULD COME FIRST?

According to the recent classification of cardiogenic shock, the classic form of cardiogenic shock (class C) is characterized by an impaired tissue perfusion that requires interventions such as inotropes, vasopressors or mechanical support (i.e. ECMO) beyond volume resuscitation to restore perfusion [52▪▪].

At time of shock recognition, prioritization between vasopressor and inotropic agents should take severity of hypotension into account. As the dominant aspect of cardiogenic shock pathophysiology is the failure of the heart to generate enough cardiac output to preserve tissue perfusion, it sounds logical to begin by the administration of an inotropic agent. Increasing cardiac output is expected to increase blood pressure, whereas increasing blood pressure is expected to compromise cardiac output in the context of a failing heart. One may hence suggest to initiate inotropes first, and to add vasopressors if hypotension persists. However, coronary artery perfusion is critically impaired when blood pressure is too low, so that the heart does not respond to inotropic stimulation in these conditions. Accordingly, in severe hypotension, inotropic and vasopressor agents should be initiated simultaneously.

CONCLUSIONS

Noradrenaline and dobutamine remain the first-line vasoactive agents in cardiogenic shock. In selected cases, vasopressin and levosimendan may represent excellent alternatives.

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Systematic review on the impact of levosimendan on weaning from VA ECMO.

49. ▪ Vally S, Ferdynus C, Persichini R, *et al.* Impact of levosimendan on weaning from peripheral venoarterial extracorporeal membrane oxygenation in intensive care unit. Ann Intensive Care 2019; 9:24.

In 150 patients under VA ECMO, administration of levosimendan facilitated weaning from ECMO.

50. ▪ Alonso-Fernandez-Gatta M, Merchan-Gomez S, Gonzalez-Cebrian M, *et al.* Levosimendan in veno-arterial extracorporeal membrane oxygenator supported patients: impact on the success of weaning and survival. Artif Organs 2021. doi: 10.1111/aor.13899.

No difference in weaning from VA ECMO in levosimendan and control patients, but the study was underpowered to detect potentially clinically significant differences (61 vs 44%).

51. ▪ Guilherme E, Jacquet-Lagrèze M, Pozzi M, *et al.* Can levosimendan reduce ECMO weaning failure in cardiogenic shock?: a cohort study with propensity score analysis. Crit Care 2020; 24:442.

No significan difference in VA ECMO weaning failure between levosomendan and control (29 vs 35%) in a propensity matched cohort.

52. ▪▪ Baran DA, Grines CL, Bailey S, *et al.* SCAI clinical expert consensus statement on the classification of cardiogenic shock: This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. Catheter Cardiovasc Interv 2019; 94:29–37.

Consensus defining the five stages of cardiogenic shock: A at risk, B beginning, C classic, D deteriorating and E extermis. Each stage is characterized by specific clinical signs, biochemical markers, hemodynamic and therapeutic features.

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